Remarks

I. Status of the Claims and Support for Amendments

By the forgoing amendments, claims 1-27, 32, 33, 39, 40, 45-47, 57-60, 63-77, 81, 82 and 87-89 have been cancelled without prejudice thereto or disclaimer thereof, as reading, at least in part, on non-elected species. Applicants reserve the right to prosecute the subject matter of these claims in one or more continuing applications.

The amendments to claims 90, 91, 93, 97, 98, 106 and 108 are sought to be entered to provide the correct dependency for these claims upon cancellation of claims 87-89. Hence, no new matter is added by the foregoing amendments and their entry and consideration are respectfully requested. Upon entry of the foregoing amendments, claims 86 and 90-110 are pending in the application, with claim 86 being the sole independent claim.

II. Summary of the Office Action

In the Office Action dated October 31, 2003, the Examiner has withdrawn claims 87-89 from consideration, and has made five rejections of the claims. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

III. The Withdrawal of Claims 87-89

In the Office Action at page 2, the Examiner has withdrawn claims 87-89 from consideration under 37 C.F.R. § 1.142(b) as allegedly being drawn to a nonelected species. Applicants respectfully traverse this withdrawal. However, for reasons unrelated to this

action and not in acquiescence thereto, claims 87-89 have been cancelled without prejudice or disclaimer. Hence, the withdrawal of these claims has been rendered moot.

IV. The First Rejection Under 35 U.S.C. § 103(a)

In the Office Action at pages 2-3, the Examiner has rejected claims 86, 90-94 and 96-107 under 35 U.S.C. § 103(a), as being unpatentable over Birkett *et al.* (U.S. Patent No. 6,231,864; document "A" cited on the Form PTO-982 attached to Paper No. 11 and Doc. No. AE2, of record; hereinafter "Birkett"), in view of Mark *et al.* (U.S. Patent No. 4,959,314; document "C" cited on the Form PTO-892 attached to Paper No.11; hereinafter "Mark") and Zhou *et al.* (document "Z" cited on the Form PTO-892 attached to Paper No. 11; hereinafter "Zhou"). Applicants respectfully traverse this rejection.

A. The Cited References Cannot Be Properly Combined

Applicants reiterate and incorporate herein by reference the remarks concerning this same rejection that were provided in Applicants' reply filed on August 7, 2003. Specifically, Birkett does not disclose the use of core particles in which the cysteine residues at positions 48 and 107 of SEQ ID NO:134 (or at positions 48 and 110 of SEQ ID NO:158) are either deleted or substituted with another amino acid, and does not disclose, suggest, or otherwise contemplate the use of a virus-like particle that is a dimer or a multimer of a polypeptide having the amino acid sequence characteristics recited in present claim 86. These deficiencies in Birkett are not cured by the disclosures of Mark or Zhou, alone or in combination, neither of which provides any suggestion or disclosure of the use of core particles having the amino acid sequence characteristics recited in present claim 86. Hence,

one of ordinary skill would have found no suggestion or motivation within the references themselves to have combined the disclosures of these references in order to attempt to make and use the presently claimed invention. Absent such suggestion and motivation, the references cannot be properly combined, and a *prima facie* case of obviousness cannot be established. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Thus, the Examiner has not met the burden required to sustain a *prima facie* case of obviousness.

Contrary to the Examiner's contentions in the Office Action, Applicants are not arguing "against the references individually" (Office Action at page 4). As the Examiner has stated, the present rejection is "based on [a] combination[] of references." *Id.* Applicants respectfully remind the Examiner, however, that the requisite motivation for combining references in attempting to establish a *prima facie* case of obviousness *must* be found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *See In re Kotzhab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). In the present case, for reasons discussed below, the disclosure of Mark provides *no* proper motivation to modify cysteine residues in HBV particles; hence, one of ordinary skill reading Birkett in view of Mark would have had no reason to have combined their disclosures to attempt to make and use the presently claimed invention.

It therefore appears that the Examiner is attempting to find the required motivation to combine the cited references in Applicants' own specification rather than in the cited art. As the Federal Circuit has held numerous times, however, such a hindsight analysis is impermissible -- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143

(Fed. Cir. 1985) ("When prior art references require selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself."); *Fine*, 5 USPQ2d at 1600 ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); *In re Pleuddemann*, 910 F.2d 823, 828 (Fed. Cir. 1990) (noting that use of an applicant's specification as though it were prior art to support an obviousness determination is legal error); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, "must be founded in the prior art, not in the applicant's disclosure."). The Board has also provided the same mandate on this issue:

> it is impermissible to use the claimed invention as an instruction manual or "template" to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious . . . . a rejection based on § 103 must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996). Thus, the use of hindsight analysis in the present case is impermissible and cannot be used to attempt to establish a *prima facie* case of obviousness.

B. The Reliance Upon Mark is Improper

Applicants also respectfully assert that the present rejection improperly relies upon

the disclosure of Mark, because Mark is non-analogous art. Specifically, the disclosure of Mark relates to problems that are totally unrelated to the problems solved by the presently claimed invention. As one of ordinary skill would readily understand, and as the Examiner has stated (*see* Office Action at page 2, third paragraph, lines 6-8), the disclosure of Mark relates to methods for reducing or eliminating undesirable intermolecular crosslinking and intramolecular disulfide bridges that can be formed in recombinant proteins, by replacing or deleting cysteine residues that are non-essential for biological activity of the proteins. These problems are wholly unrelated to those solved by Applicants in making the presently claimed invention.

As the disclosure of Mark clearly demonstrates (*see* Mark at col. 1, lines 30-44 and 53-60), the problems to be solved in that reference can be summarized as follows: when a protein is microbially produced, its free cysteines are usually involved in the formation of intermolecular crosslinks and intramolecular disulfide bridges which lead to the formation of dimers and oligomers in the microbial extracts, which in turn renders purification and separation of the protein very laborious and time-consuming and necessitates several additional steps in purification, such as reducing and reoxidizing the protein. In addition, formation of multimers and random intramolecular disulfide bridges may lead to low specific biological activity. Hence, the problem to be solved in Mark is the propensity of recombinant proteins (particularly interferon-beta ("IFN-β")) to undergo random intermolecular crosslinking or intramolecular disulfide bridge formation, between cysteines on the protein molecules, to overcome the difficulties in purification and the reduction in biological activity that often accompany the formation of such cysteine-cysteine interactions.

Unlike those of IFN-β described in Mark, however, the free cysteines of HBcAg are

not reported to undergo undesirable intermolecular crosslinking or intramolecular interactions via formation of disulfide bridges. Instead, the problem addressed by removal of the cysteine residues from HBcAg according to the presently claimed invention is quite different. Specifically, by the present invention Applicants have discovered that if free cyteines are present and accessible on a virus-like particle, these cysteines may provide binding sites for toxic products. *See* Specification as filed at pages 36-37, paragraphs 0143-0146. As described in the present specification, and as one of ordinary skill would readily understand, the administration to an individual of a HBcAg conjugate containing toxic components could lead to a potentially serious adverse reaction (*see* Specification as filed at page 36, paragraph 0144, final sentence).

Additionally, as noted above, the disclosure of Mark relates to disulfide bonds formed between two cysteines, either within a single protein molecule (intramolecular disulfide bridging) or between two different protein molecules (intermolecular crosslinking via disulfide bridging). This situation is quite different from that in the presently claimed invention, where intermolecular crosslinks are formed via the interactions between cysteine residues and lysine residues when hetero-bifunctional cross-linkers are used. Specifically, in one embodiment of the presently claimed invention, a hetero-bifunctional cross-linker was employed which is reactive both with amino groups (*e.g.*, those on lysine residues) and with sulfhydryl groups (*e.g.*, those on cysteine residues). In this scenario, the sulfhydryl groups of free cysteines on the core particle may react through cross-linkers linked to the amino groups of lysine residues in the vicinity, thereby resulting in a plurality of undefined cross-linked species of HBcAg monomers (*i.e.*, a diverse mixture of cross-linked monomeric HBcAgs) (*see* Specification at page 37, paragraph 146). The presence of such a mixture of undefined

molecules creates great difficulty in assessing the coupling efficiency, and renders uncertain the exact composition of the vaccine. As noted above, however, the reaction leading to such crosslinked mixtures is different from that disclosed in Mark with respect to intermolecular crosslinking which is the result of the formation of disulfide bonds between two sulfhydryl groups on free cysteines (rather than between a sulfhydryl group and an amino group).

There is a fundamental difference between a disulfide bridge such as that addressed in Mark, and a covalent link made using a hetero bifunctional agent such as that addressed by the presently claimed invention. As one of ordinary skill is aware, disulfide bridge crosslinks can be broken or rearranged by the use of thiol agents or reducing agents such as dithiothreitol (DTT) or β-mercaptoethanol. That is not the case for crosslinks between protein molecules or subunits that are formed via reaction between lysine and cysteine residues on the protein through use of a heterobifunctional agent such as MBS. In this case, if free cysteines from one subunit react with a lysine of another subunit within the same particle, dimers are produced. Those dimers may react further with one or more additional molecules or subunits, leading to the formation of increasingly large multimers within the same particle. As described in the present application (and as referenced above), these multimers lead to problems while analyzing the vaccine, *e.g.*, by SDS-PAGE, and cannot be broken or rearranged using thiol agents or reducing agents. Hence, the crosslinking problem addressed in Mark is significantly different (and indeed, significantly more easily solved) than the crosslinking problem addressed by the presently claimed invention.

Since Applicants teach the use the compositions of the presently claimed invention as vaccines, the purity as well as the toxicity of the vaccines are of great concern in the present invention. In contrast, the disclosure of Mark does *not* address the toxicity of the

proteins produced therein, and only addresses purity from the standpoint of minimization of disulfide bridges rather than crosslinking between cysteine and lysine residues. Accordingly, one of ordinary skill would have found no guidance in Mark as to how to address the problem of the linkage of toxic compounds to proteins via free cysteine residues, nor the problem of minimizing the formation of cysteine-lysine crosslinks, since Mark was not directly concerned with those problems.

Lastly, the proteins disclosed in Mark are of a very limited class. Specifically, a number of cytokines are disclosed in Mark as examples (*see* Mark at col. 3, line 65, to col. 4, line 1), and the bulk of the disclosure of that reference relates to IFN-β, TNF-α and IL-2. Mark does *not* even mention viral particles or components thereof, particularly HBcAg, let alone the cysteine properties of HBcAg. Indeed, Mark fails to recognize the specifics of particles formed from the assembly of multiple copies of the same or of a small number of different subunits. The proteins described in Mark, such as TNF-α, IFN-β or IL-2, may form dimers or trimers, but these complexes are far from being macromolecular assemblies of the type formed by HBcAg.

For at least the foregoing reasons, Applicants respectfully assert that the disclosure of Mark is not analogous art with respect to the presently claimed invention -- it is neither in the same field of endeavor (since it does not address the issues germane to cysteine-lysine crosslinking in viral particles, particularly HBcAg), nor is it reasonably pertinent to the particularly problem with which the present invention is concerned (since it does not address issues germane to linkage of toxic compounds to viral particles, particularly HBcAg, via free cysteines). Without being in the same field of endeavor and without being directed to the same problem as the presently claimed invention, Mark cannot be used to support an

obviousness rejection. *See In re Clay*, 966 F.2d 656, 658-9 (Fed. Cir. 1992); *see also Ex parte Campbell*, 211 USPQ575, 576 (USPTO BPAI 1980) ("[a]lthough the solution to the problem would have been obvious once recognized, none of the prior art before us indicates any recognition of the existence of the problem."). Accordingly, Applicants respectfully assert that Mark would not be regarded as analogous art by one of ordinary skill in the fields to which the present invention pertains. For at least these reasons, the reliance upon Mark in making the present rejection is improper.

C. The Disclosure of Zhou Does Not Cure the Deficiencies in Birkett

Since Mark is not available as prior art, the present rejection can only be based on Birkett in view of Zhou. Applicants respectfully assert that this combination of references also does not render obvious the presently claimed invention, since Zhou does not cure the above-noted deficiencies in Birkett. Zhou discloses that *all* of the HBV core cysteines are non-essential for assembly of core particles. Zhou's focus is also on intermolecular disulfide bridges as in Mark, and their role in capsid assembly. Zhou does not disclose the *specific* deletion or substitution of CYS residues 48 and 110 of SEQ ID NO:158 as required in the presently claimed invention. Therefore, one of ordinary skill in the art would not have taken Zhou into account for solving the problems solved by the present invention (as discussed above for Mark). Moreover, Zhou does not suggest or otherwise contemplate the deletion *only* of Cys48 and Cys110 SEQ ID NO: 158, while retaining the other cysteine residues, *e.g.*, Cys61. Hence, Applicants respectfully assert that Zhou cannot be properly combined with Birkett to render the claimed invention obvious.

D. The Cited Art Does Not Suggest Making the Necessary Molecular Modifications

The Examiner is also reminded that it is axiomatic that, in order to support a *prima facie* case of obviousness, the prior art must suggest making the *specific* molecular modifications necessary to achieve the claimed invention. *See In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Lalu*, 747 F.2d 703, 705 (Fed. Cir. 1984) ("[t]he prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). That is, simply because "one can conceive a general process in advance for preparing an *undefined* compound [*e.g.*, a core particle comprising a 'Hepatitis B amino acid sequence'] does not mean that a claimed *specific* compound [*e.g.*, a core particle comprising SEQ ID NO:134 or SEQ ID NO:158 (or portions thereof) which is modified so that the cysteine residues at positions 48 and 107 of SEQ ID NO:134 (or 48 and 110 of SEQ ID NO:158) are either deleted or substituted with another amino acid'] was precisely envisioned and therefore obvious." *Deuel* at 1559. Thus, in order for Birkett, Mark and Zhou to be suitable as references upon which to base a *prima facie* case of obviousness, there must be, at a minimum, a teaching or suggestion in these references that would have compelled one of ordinary skill in the art to include in their core particles a polypeptide having the amino acid characteristics recited in claim 86, which are substantially different from those of the HBV sequences disclosed in these references. As noted above, such a teaching or suggestion is wholly lacking in the cited references, alone or in combination -- that is, the *specific* sequences recited in claim 86 (and the remaining claims depending therefrom that are the subject of the present rejection) are not disclosed, suggested or otherwise contemplated in the cited references, alone or in

combination. Therefore, in view of the holdings in *Deuel* and *Lalu*, the cited references cannot support a *prima facie* case of obviousness of the presently claimed invention.

E. Summary

In view of the foregoing remarks, Applicants respectfully assert that a *prima facie* case of obviousness has not been, and indeed cannot be, established on the basis of the disclosures of Birkett in view of Mark and Zhou. Reconsideration and withdrawal of the rejection of claims 86, 90-94 and 96-107 over these references therefore are respectfully requested.

V. The Second Rejection Under 35 U.S.C. § 103(a)

In the Office Action at page 3, the Examiner has rejected claim 95 under 35 U.S.C. § 103(a) as being unpatentable over Birkett in view of Mark and Zhou and further in view of Neurath *et al.* (U.S. Patent No. 5,565,548; document "B" cited on the Form PTO-892 attached to Paper No. 11; hereinafter "Neurath"). Applicants respectfully traverse this rejection.

Applicants reiterate and incorporate herein the remarks made above concerning the combination of the disclosures of Birkett, Mark and Zhou. Specifically, Birkett is deficient as a primary reference, Mark is nonanalogous art and therefore cannot be used in an obviousness rejection of the presently claimed invention, and Zhou does not cure the deficiencies of Birkett. Neurath only addresses immunogenic complexes containing certain HBV peptides and other immunogens, but does not indicate that such complexes present the immunogens in an ordered and repetitive array as required by the presently claimed

invention. Thus, one of ordinary skill would have found no motivation to combine the disclosure of Neurath with those of Birkett and Zhou (and Mark, which in any event is not available as a reference against the presently claimed invention). Hence, the disclosures of Birkett, Mark, Zhou and Neurath cannot be properly combined, and in any event would not have rendered the presently claimed invention obvious.

In view of the foregoing remarks, Applicants respectfully assert that a *prima facie* case of obviousness has not been, and indeed cannot be, established on the basis of the disclosures of Birkett in view of Mark and Zhou and further in view of Neurath. Reconsideration and withdrawal of the rejection of claim 95 over these references therefore are respectfully requested.

VI. The Third Rejection Under 35 U.S.C. § 103(a)

In the Office Action at page 3, the Examiner has rejected claims 108-110 under 35 U.S.C. § 103(a) as being unpatentable over Birkett in view of Mark and Zhou and further in view of Davis *et al.* (WO 98/40100; document "N" cited on the Form PTO-892 attached to Paper No. 11; hereinafter "Davis"). Applicants respectfully traverse this rejection.

Applicants reiterate and incorporate herein the remarks made above concerning the combination of the disclosures of Birkett, Mark and Zhou. Specifically, Birkett is deficient as a primary reference, Mark is nonanalogous art and therefore cannot be used in an obviousness rejection of the presently claimed invention, and Zhou does not cure the deficiencies of Birkett. Davis only addresses immunogenic complexes containing certain HBV peptides and alum as an adjuvant, but does not indicate that such complexes present the immunogens in an ordered and repetitive array as required by the presently claimed

invention. Thus, one of ordinary skill would have found no motivation to combine the disclosure of Davis with those of Birkett and Zhou (and Mark, which in any event is not available as a reference against the presently claimed invention). Hence, the disclosures of Birkett, Mark, Zhou and Davis cannot be properly combined, and in any event would not have rendered the presently claimed invention obvious.

In view of the foregoing remarks, Applicants respectfully assert that a *prima facie* case of obviousness has not been, and indeed cannot be, established on the basis of the disclosures of Birkett in view of Mark and Zhou and further in view of Davis. Reconsideration and withdrawal of the rejection of claims 108-110 over these references therefore are respectfully requested.

VII. The First Obviousness-Type Double Patenting Rejection

In the Office Action at page 4, the Examiner has provisionally rejected claims 86 and 90-110 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 100-114 of commonly owned, co-pending U.S. Appl. No. 10/050,902 ("the '902 application"). Applicants respectfully traverse this rejection. However, to expedite prosecution, Applicants respectfully request that this rejection be held in abeyance until the identification of otherwise allowable subject matter in the present application, at which time Applicants will consider filing a properly executed Terminal Disclaimer Under 37 C.F.R. § 1.321(c).

VIII. The Second Obviousness-Type Double Patenting Rejection

In the Office Action at page 4, the Examiner has provisionally rejected claims 86 and 90-110 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-16 of the '902 application. Applicants respectfully traverse this rejection. However, to expedite prosecution, Applicants respectfully request that this rejection be held in abeyance until the identification of otherwise allowable subject matter in the present application, at which time Applicants will consider filing a properly executed Terminal Disclaimer Under 37 C.F.R. § 1.321(c).

IX. Conclusion

All of the stated grounds of rejection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt entry and consideration of the present Amendment and Reply, and allowance of all pending claims, are earnestly solicited.

Respectfully submitted,

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